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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,596	01/16/2001	Johannes Dirk Anthonie Van Embden	41497	1209

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EXAMINER	
SOUAYA, JEHANNE E	
ART UNIT	PAPER NUMBER
1634	11

DATE MAILED: 07/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/647,596	Applicant(s) VAN EMBDEN ET AL.	
	Examiner Jehanne Souaya	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Currently, claims 1-25 are pending in the instant application. Applicant's arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The specification contains an embedded hyperlink and/or other form of browser-executable code (p. 8 line 38). The examiner has disabled the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01

Maintained Rejections

4. Claims 1-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Embden et al (WO 95/31560) and Accession numbers M27059 and M27060.

The claims are drawn to a method for the in vitro amplification of nucleic acids and the detection and differentiation of bacteria using primers that are sufficiently complementary to a

part of the Direct Repeat sequence of *E.coli*, wherein the Direct Repeat is between 20-50 base pairs and occurs 5-60 times in the region of the bacterial genome and wherein the direct repeat sequences are separated by spacer sequences with a length between 20-50 nucleotides.

Van Embden et al teaches a method for the in vitro amplification of nucleic acids , the detection of M. tuberculosis, and the differentiation of *M. tuberculosis* from other bacteria, using amplification primers wherein a pair of primers is used comprising oligonucleotides sequences sufficiently complementary to a part of the direct repeat sequence of a bacterium belonging to the *M. tuberculosis* complex of microorganisms (see abstract). Van Embden teaches that due to the multiple presence of direct Repeats in the microorganisms to be detected, the use of such primers implies that all the spacer regions will be amplified in an n efficient manner (see p. 7). Van Embden teaches that in particular it is not necessary for extremely long sequences to be produced in order to obtain amplification of spacers located at a distance form the primer. Van Embden teaches that with the selection of the pairs a heterogenous product is obtained comprising a lot of smaller fragments all comprising spacer region nucleic acid. Van Embden teaches that subsequently the detection of the amplified product can occur simply by using an oligonucleotide probe directed at one or more of the spacer regions one wishes to detect and that in order to avoid hindrance in the amplification reactions the primers can have oligonucleotide sequences complementary to non-overlapping parts of the direct repeat sequence so that when both primers hybridize to the same direct repeat and undergo elongation they will not be hindered by each other. Van Embden further teaches that in particular to avoid any hindrance during elongation

reactions when one primer DRA is capable of elongation in the 5' direction and the primer DRB is capable of elongation in the 3' direction, the DRA is selected such that it is complementary to a sequence of the Direct Repeat located to the 5' side of the direct repeat to which DRb is complementary. Van Embden further teaches that a probe can be used to carry out the invention wherein the probe is capable of hybridizing to a spacer sequence and comprises at least 7 consecutive nucleotides homologous to the spacer sequence and/or exhibiting at least 60% homology with the spacer. Van Embden teaches primers, probes, and kits to carry out the method of the invention.

Although Van Embden does not teach such amplifying, detecting or differentiating *E. coli* using primers to the direct repeat sequence of *E. coli*, such a sequence was known and taught in the art at the time of the invention. Applicant's own specification discloses such knowledge and teaches Genbank Accession numbers M27059 and M27060 which teach the region of E.coli comprising the direct repeat sequences. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Van Embden for the purpose of detecting and differentiating *E. coli* from other bacteria as Van Embden an efficient method of doing so for *M. tuberculosis* complex bacteria. The ordinary artisan would have been motivated to modify the method of Van Embden to detect *E. coli* with the general method taught by Van Embden as the state of the art is very high with regard to detecting and differentiating *E. coli* as well as other bacteria for purposes such as diagnosis of specific infection.

With regard to claim 2, which is drawn to the limitation of using the program Patscan to obtain the Direct Repeat sequence, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to automate screening for a direct repeat sequence from a bacteria for the purpose of optimizing and obtaining the best possible sequence for use in a method to differentiate and detect a specific bacteria from other bacteria. The state of the art at the time of the invention was very high with regard to determining sequences with similarities and differences between different bacteria for the purpose of differentiating and detecting specific types of bacteria. As the Patscan program was known and readily available at the time of the invention, the ordinary artisan would have been motivated to automate the screening of a bacterial genome to obtain the best possible sequence from the direct repeat region for the purpose of detecting and differentiating a specific bacteria. SEE MPEP 2144.04 which states:

> III. AUTOMATING A MANUAL ACTIVITY
> In re Venner, 262 F.2d 91, 95, 120 USPQ 193, 194 (CCPA 1958) (Appellant argued that claims to a permanent mold casting apparatus for molding trunk pistons were allowable over the prior art because the claimed invention combined "old permanent-mold structures together with a timer and solenoid which automatically actuates the known pressure valve system to release the inner core after a predetermined time has elapsed." **The court held that broadly providing an automatic or mechanical means to replace a manual activity which accomplished the same result is not sufficient to distinguish over the prior art.).**

With regard to claim 7 which is drawn to the limitation that the direct repeat sequence is not prone to loop formation or any obvious secondary structure, it would have been prima facie obvious to one of ordinary skill in the art to target a sequence that was not prone to loop

formation or any obvious secondary structure as it was well known in the art at the time the invention was made that such secondary structure could inhibit or undermine methods relying on specific hybridization of a probe or primer to a target sequence.

Response to Arguments

5. The response traverses the rejection. The arguments have been thoroughly reviewed but were not found persuasive. The response traverses that there is no motivation to combine the respective teachings of the references. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it was known in the art, as specifically taught in applicant's specification (see p. 8, lines 26-30) that repeat patterns existed in *E. coli*. This available knowledge was cited by the examiner in the previous office action on page 5, lines 1-3. The sequences containing these repeat patterns were also taught in the art and available to the ordinary artisan. The examiner cited such sequences in the previous office action. Furthermore, it was generally known in the art at the time of applicants invention that there was a need for detecting *E. coli* and a very large number of studies were conducted prior to applicant's invention

using DNA amplification and hybridization to detect different bacterial species and strains, including *E. coli*. Therefore, with this knowledge readily available, it would have prima facie obvious to one of ordinary skill in the art to detect *E. coli* using a region of repeating nucleotide patterns as Van Embden teaches the successful detection of *Mycobacterium* by exploiting the repeating nucleotide patterns that it possessed.

The response further traverses that the ordinary artisan would not have had a reasonable expectation of success for achieving the present invention due to the large number of microorganisms in which the DR pattern is not present. This argument has been thoroughly reviewed but was not found persuasive because it was already known in the art at the time of applicants invention that *E. coli*, as well as other microorganisms possessed repeating nucleotide patterns (see specification, p. 8, lines 26-30). In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The response traverse that the *E. coli* sequence is not the same as the *M. tuberculosis* DR sequence and that the identity of the DRs between categories of microorganisms differs. This argument has been thoroughly reviewed but was not found persuasive. Firstly, the argument that

the *E. coli* sequence is not the same as the *M. tuberculosis* sequence is not understood because if they were the same, the ordinary artisan could not use them to differentiate between microorganisms or to specifically detect a single microorganism in a pool of unknowns. Secondly, the art teaches and the specification acknowledges such, that repeating patterns of nucleotides were present in *E. coli* as well as other microorganisms. Therefore, the art provides sufficient motivation to exploit repeating nucleotide patterns to detect microorganisms as Van Embden teaches the successful detection of *M. tuberculosis* by using repeating nucleotide patterns.

The response traverses that if a person skilled in the art is interested in looking at *E. coli* diagnosis, the person would not look at literature describing *Mycobacterium*. This argument has been thoroughly reviewed but was not found persuasive. It has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, detection of *E. coli* and *Mycobacterium* using nucleotide analysis is in the same field of nucleotide analysis to detect microorganisms. Further, using genetic analysis to detect *E. coli* is pertinent to the problem solved by using genetic analysis to detect *Mycobacterium* as both are infectious microorganisms and it is generally known in the art that methods of detecting such microorganisms are needed and useful.

The response traverses that if one of ordinary skill in the art were to have tried to use the method for *Mycobacterium tuberculosis* strain differentiation to determine strain differentiation and other microorganisms, one of ordinary skill would have found no matches and would have considered this as evidence that the method was specific for *Mycobacterium tuberculosis*. This argument has been thoroughly reviewed but was not found persuasive. If the ordinary artisan had tried to use the primers and probes taught for *Mycobacterium* analysis to detect other microorganisms and found no matches, it would have been apparent to the ordinary artisan that the particular sequences used were specific for *Mycobacterium* analysis, which would have been in keeping with Van Embden's method of differentiating between *Mycobacterium*. The ordinary artisan would not have thought that using repeat patterns to detect different microorganisms would not have worked. On the contrary, the artisan would have realized that the sequences taught by Van Embden were specific for *Mycobacterium*. Given the successful differentiation taught by Van Embden, the ordinary artisan would have been motivated to use the general method taught by Van Embden to detect other microorganisms that have nucleotide repeat patterns. There was a reasonable expectation that other microorganisms possessed nucleotide repeat patterns because it was known in the art at the time of the invention, as acknowledged by the specification, that repeating patterns of nucleotides existed in *E. coli* as well as other microorganisms (see p. 8).

For these reasons and the reasons made of record of above and in previous office actions, the rejection is maintained.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. No claims are allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
Art Unit 1634
July 9, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600